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## The impact of new vaccine introduction on immunization and health systems: A review of the published literature

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### Abstract

We conducted a systematic review of the published literature to examine the impact of new vaccine introduction on countries' immunization and broader health systems. Six publication databases were searched using 104 vaccine and health system-related search terms. The search yielded 15,795 unique articles dating from December 31, 1911 to September 29, 2010. Based on review of the title and abstract, 654 (4%) of these articles were found to be potentially relevant and were referred for full review. After full review, 130 articles were found to be relevant and included in the analysis. These articles represented vaccines introduced to protect against 10 different diseases (hepatitis A, hepatitis B, *Haemophilus influenzae* type b disease, human papilloma virus infection, influenza, Japanese encephalitis, meningococcal meningitis, *Streptococcus pneumoniae* disease, rotavirus diarrhea and typhoid), in various formulations and combinations. Most reviewed articles (97 [75%]) reported experiences in high-income countries. New vaccine introduction was most efficient when the vaccine was introduced into an existing delivery platform and when introduced in combination with a vaccine already in the routine childhood immunization schedule (i.e., as a combination vaccine). New vaccine introduction did not impact coverage of vaccines already included in the routine childhood immunization schedule. The need for increased cold chain capacity was frequently reported. New vaccines facilitated the introduction and widespread use of auto-disable syringes into the immunization and the broader health systems. The importance of training and education for health care workers and social mobilization was frequently noted. There was evidence in high-income countries that new vaccine introduction was associated with reduced health-care costs. Future evaluations of new vaccine introductions should include the systematic and objective assessment of the impacts on a country's immunization system and broader health system, especially in lower-income countries.

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<sup>1</sup>See Appendix A.

## Keywords

New vaccines; Under-utilized vaccines; Introduction; Immunization program; Health system

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## 1. Introduction

The Expanded Program on Immunization (EPI) was established by the World Health Organization (WHO) in 1974 to provide protection against six vaccine-preventable diseases (tuberculosis, poliomyelitis, diphtheria, tetanus, pertussis, and measles) through routine infant immunization. Since then, many new vaccines have become available, and global public funding for immunization, including the GAVI Alliance, has increased accessibility to these vaccines [1]. Most of the new vaccines, including hepatitis B (HepB) vaccine, *Haemophilus influenzae* type B (Hib) vaccine, pneumococcal conjugate vaccine (PCV), and rotavirus (RV) vaccine are intended to be included in the routine childhood immunization schedule. Other new vaccines, such as human papillomavirus (HPV) vaccine meningococcal vaccine, yellow fever vaccine, and typhoid vaccine are intended for older or at-risk populations.

The introduction of a new vaccine can have both positive and negative impacts on the immunization system and the broader health system. It may provide opportunities and resources to strengthen an existing system, or it may add stress to an already weak infrastructure. Based on a request in 2010 from the Strategic Advisory Group of Experts (SAGE) on Immunization that guides the World Health Organization (WHO) on global immunization policies, we conducted a systematic review of the published literature to examine evidence of impact of new vaccine introduction on health and immunization systems reported in the medical literature.

## 2. Methods

### 2.1. Search strategy

We developed search terms to identify articles that included information describing the impact of new vaccine introduction on immunization systems and health systems [2] (Table 1). The terms were selected to be inclusive and were developed with input from immunization experts. The search terms were divided into two broad categories: (1) vaccines and (2) immunization and health systems, and databases were searched to identify articles captured by at least one search term in each category (Table 1).

We searched seven publication databases (Medline®, Embase™, Nursing Update, West African Journal of Nursing, CINAHL®, Web of Science®, and Global Health) that are relevant to vaccines and immunization programs, and are likely to contain reports from low income countries. We attempted to use identical terms to search each database; however, as each database had certain specifications, it was sometimes necessary to modify some terms. We limited the search to reports involving human subjects, published in any language. The final search date was September 29, 2010 and was not limited to a beginning year.

## 2.2. Inclusion criteria

We reviewed the title and abstract of each article identified using the search strategy to determine whether the article was potentially relevant (i.e., contained quantitative or qualitative information on the impact of new vaccine introduction on the immunization system, the broader health system, or both). Potentially relevant articles were referred for a full abstraction. Articles that discussed disease incidence, disease burden, vaccination coverage, serotype replacement, immunization campaigns, or adverse events following immunization were included if they contained data or discussion of vaccine impact on the health or immunization system and assessed outcome within the first five years after vaccine introduction, unless the assessed outcome manifested more than five years after vaccine introduction (e.g., HepB vaccine and hepatocellular carcinoma or cirrhosis, or HPV vaccine and cervical cancer). Cost effectiveness studies were considered if they included real-time data, and real situations and savings and were not based on results of modeling. Expert opinion articles were included if data were reported. We excluded clinical trials, because they did not show impact on the immunization and health systems following vaccine introduction.

## 2.3. Abstraction process

We used EndNote X3.0.1S (Thompson Reuters) to organize and track the articles, adding databases sequentially beginning with Medline, and performing automated and manual de-duplication following the addition of each subsequent database. Each article was reviewed to determine if it addressed the impact of the vaccine introduction on the immunization and health system. Sixteen immunization experts from the World Health Organization (WHO), the Centers for Disease Control and Prevention (CDC), The United Nations Children's Fund (UNICEF), the London School of Hygiene and Tropical Medicine and Hygiene (LSHTM), the Program for Appropriate Technology in Health (PATH), and Maternal and Child Health Integrated Program (MCHIP) participated in the abstraction process. Information from relevant articles was abstracted using a Microsoft Access® 2007 data collection form and were organized according to the WHO Framework for Action (Fig. 1); this framework was created by WHO in 2007 to promote a common understanding of health care systems by providing a systematic means for considering the essential functions [2]. The Framework comprises six building blocks: service delivery; health workforce; information; medical products, vaccines and technologies; financing; and leadership and governance. Countries were grouped by gross national income into categories according to the World Bank Atlas Method [<http://data.worldbank.org/about/country-classifications/country-and-lending-groups>]. Non-English articles were reviewed and abstracted by native speakers, whenever possible. A random sample of 10% of the articles were reviewed and abstracted by a second reviewer. If discordance was found, the article was reviewed by the first author to resolve discrepancies.

## 3. Results

### 3.1. Search and abstraction

The search yielded 24,768 articles from December 31, 1911 to September 29, 2010, among which 8973 (36%) were found to be duplicates (Fig. 2). Reviewers applied the inclusion

criteria to the remaining 15,795 titles and abstracts. Among these, 654 (4%) articles met the inclusion criteria and were referred for full abstraction; 49 (7%) of these were in languages other than English. One hundred twenty-nine (20%) of the 654 abstracted articles were found to be relevant for the analysis. In addition, one key article known to the authors that was not identified by the systematic search of the published literature was included, resulting in a total of 130.

### 3.2. General overview

Among the 130 studies included in this review (Table 2), 97 (75%) were from high income countries; 21 (16%) were from middle income countries; and 4 (3%) were from low income countries. The studies included vaccines targeting 10 diseases (hepatitis A (3 [2%]), hepatitis B (24 [19%]), Hib disease (28 [22%]), HPV infection (13 [10%]), influenza (1 [1%]), Japanese encephalitis (1 [1%]), meningococcal meningitis (17 [13%]), *Streptococcus pneumoniae* disease (28 [22%]), rotavirus diarrhea (14 [11%]) and typhoid (2 [2%])). Multiple vaccine formulations (i.e., antigens, adjuvants, stabilizers, preservatives and other components) and vaccine combinations were represented in the studies. Overall, 64 (56%) studies considered vaccine introductions that took place between 2000 and 2008.

### 3.3. Service delivery

In a number of countries, introduction of the new vaccines required new delivery strategies or modification of existing delivery strategies. While many new vaccines have been introduced through routine vaccination programs and mass campaigns, other delivery strategies, including one-time catch up vaccination, school-based vaccination, or a combination of strategies, depending on the vaccine and age recommendation for vaccination have been utilized to introduce new vaccines [3-10]. Novel delivery strategies, and the need for social promotion and education about the new vaccine's safety and potential adverse events, may also affect the delivery of other immunization and health services. In several high and middle income countries coverage with existing vaccines administered through routine childhood or school-based strategies increased (Australia, Germany and Peru) or remained the same (Thailand and the United States) when new vaccines were introduced [11-16]. In Canada, offering PCV at no cost helped to remove existing inequities in PCV distribution [17], increased PCV acceptance and improved on-time vaccination [17,18]. Australia's government-funded HPV vaccination strategy consisted of school-based routine vaccination of 12-year-old girls, including a 2-year catch-up strategy [5]. The catch-up strategy for 13–18 year olds was largely school-based, and for 18–26-year-old women was carried out by general practitioners. The general practitioner visit was also intended to provide an opportunity for physicians to broaden sexual health education and discuss cervical cancer prevention [5]. However, ensuring completion of the series for those who missed school-based vaccination required additional efforts, including coordination with general practitioners, additional mop-up campaigns at the end of the year, or establishing an individual recall system.

Communication and education activities were often coupled with delivery of new vaccines. Social mobilization to publicize vaccination – including through mothers' clubs and professional organizations – was part of successful efforts to ensure wide acceptance of

HepB vaccine in Singapore [19], China [20], Taiwan [21] and Peru [15], and of Hib vaccine in Uruguay, Chile, Qatar, and Kuwait [22]. Introduction of HPV vaccine in the UK involved engagement of multiple stakeholders and was facilitated through the establishment of an HPV vaccine implementation group [23]. Knowledge and education about the disease and the vaccine, including safety issues, aided the successful introduction of Hib [24] vaccine and HepB vaccine [25] vaccine in Canada and Hib in the United Kingdom [26]. In the United States and Canada, HPV vaccine, in contrast to other routinely recommended childhood immunizations, was actively marketed through direct consumer advertising and public awareness campaigns that targeted legislators and policy makers in addition to consumers [27]. In the United Kingdom, funding for media communication about meningococcal conjugate C vaccine was included in the budget for vaccine introduction [28]. Because adding a new immunization can result in an additional injection during a routine childhood vaccination visit, immunization planners in Israel chose a Hib vaccine with a 2-dose rather than a 3-dose series, in part to avoid three injections at the 6 month visit [29]. In Australia, some vaccine providers were reported to be reluctant to administer three injections at one time, resulting in lower uptake of PCV in a high-risk population [30].

### 3.4. Health workforce

There was variability in the impact of new vaccine introduction on the health workforce. In settings where vaccination was introduced into regularly scheduled clinics, little impact on staffing and appointment times was observed, as was the case with Hib vaccine introduction in Sweden [31], HPV vaccine introduction in Australia [32], and PCV introduction in the United States [11]. Vaccine introduction into adolescent and adult immunization programs sometimes required additional staff or adjustment of appointment times: in Scotland, adding pneumococcal vaccine to appointments for influenza vaccination among older adults increased consultation times by about 2 min [33]. Additional staff were needed for HPV vaccine introduction in the United Kingdom [34], where public health nurses, pediatric nurses, health visitors, and managers were recruited into teams, and additional funding was made available to address a shortage of school nurse vaccinators. Lack of staff was reported as a barrier to HPV vaccine introduction in remote areas of Australia [5], and HepB vaccine introduction in juvenile justice facilities in the United States [35].

Training of health staff at national, regional and local levels was required for successful HepB vaccine introduction in China [36] and Zimbabwe [37], hepatitis A and Japanese encephalitis (JE) vaccine in China [38], Hib vaccine in the Americas [39,40], and meningococcal polysaccharide vaccine in Egypt [3]. When the new vaccine was introduced as a combination product that included a vaccine already used in the childhood vaccination schedule [22], training was relatively straightforward. In Zimbabwe the introduction of HepB vaccine also included development of communication materials, and training on community mobilization activities [37]. In Indonesia, training, and periodic re-training in the local language were needed to successfully implement the school-based typhoid program [10]. Continuing education was conducted in Italy to promote the birth dose of HepB vaccine [41]. To ensure funding for training, the vaccine introduction budget for HepB and Hib vaccines in Ethiopia included a training and education component [42].

### 3.5. Information

In other countries, vaccine introduction stimulated the development of new surveillance or vaccine registry systems, including comprehensive surveillance for meningococcal meningitis in the United Kingdom [4], pediatric invasive pneumococcal disease in Canada [43], hepatitis B virus-associated nephropathy in South Africa [44], and an HPV immunization registry in Australia [16,45]. In Chile and Uruguay, Hib case definitions and disease reporting forms were standardized, and a technology transfer program was developed following Hib vaccine introduction [39]. A national immunization register, implemented at the same time as a meningococcal conjugate B vaccination campaign in New Zealand, was used to monitor coverage, safety and effectiveness assessments [46]. In Australia's HPV vaccination program, a time-limited incentive payment of \$6 per notification of vaccination was offered to general practitioners to improve completeness of the vaccine register [45]. In China [47,48], Malawi [49], South Africa [50], Nicaragua [51], Canada [52] and Egypt [3], existing disease surveillance systems were used for impact evaluation, policy formulation, and program advocacy related to immunization against HepB [48], JE [47], Hib [49,50], rotavirus diarrhea [51], pneumococcal pneumonia [52] and meningococcal meningitis [3,3].

### 3.6. Medical products, vaccines and technologies

The availability and use of new technologies, including combination vaccines and auto-disable (AD) syringes, had an impact on the immunization system. In Chile (DTP-Hib) [53], the United States (DTP-Hib) [54] and Zimbabwe (DTP-HepB) [37], use of combination vaccines resulted in fewer injections, and the need for fewer needles and syringes; lower administrative costs; and reduced storage capacity, compared with introducing a new vaccine as a separate vaccine injection. Introduction of DTP-Hib vaccine in The Gambia; however, resulted in initial interruption of routine DTP immunization due to irregular supply of the combination vaccine [55].

In some instances, introduction of new vaccines created additional requirements for cold chain and logistics systems. In Ethiopia, the replacement of 10-dose vials of whole cell diphtheria–tetanus–pertussis (DTwP) vaccine with single-dose vials of pentavalent (DTwP–Hep B–Hib) increased transport and cold chain requirements [42]. The need for additional cold chain capacity was also reported for rotavirus in several Latin American countries [56], hepatitis A and B vaccine introduction in China [20,38], HPV vaccine introduction in the United States [35], and 23-valent pneumococcal polysaccharide vaccine (PPV23) for older adults in Scotland [33]. In other cases, as was the case for Hib introduction, existing infrastructure was adequate for introduction [39].

As part of new vaccine introduction, AD syringes, safety boxes, and injection safety policies were introduced into immunization programs. In an evaluation of 58 countries eligible for funding from the GAVI Alliance that received injection safety support, all but two continued exclusive use of AD syringes and safety boxes after funding ended [57,58]. In some countries, the use of AD syringes, safety boxes, and injection safety policies were expanded beyond the immunization program to other health services. Most countries were able to continue the use of AD syringes after GAVI funding for injection safety support ended.

### 3.7. Financing and sustainability

Cost was a consideration in planning new vaccine introduction, including introduction in developed countries [57]. Utilizing existing infrastructure or combination vaccines reduced the costs for introduction, as was documented with introduction of DTP-Hib in the US [54], combination HepA/HepB vaccines in Spain [58], and Hib vaccine in Sweden [31]. In a number of settings, insufficient funding [22] and loss of donor support [37] resulted in vaccine shortages and program interruptions.

A decrease in ambulatory consultations and hospitalizations, disease-related complications, and long-term sequelae associated with diseases prevented by the newly introduced vaccines was reported from developing and industrialized countries; these led to reductions in health care utilization, and in some cases resulted in changes in treatment recommendations [31,44,55,59-89] (Table 3). The introduction of PCV in the United States resulted in a decrease in the mortality in sickle cell patients; however, guidelines for penicillin prophylaxis remained unchanged, because not all pneumococcal serotypes are covered by currently available vaccines [90]. In Brazil, all-cause diarrhea costs declined following introduction of RV vaccine, but they were not sufficient to offset the costs of program implementation [82]. Targeted strategies to vaccinate high-risk populations reduced or eliminated racial and ethnic disparities in rates of Hib disease incidence in Israel [91] and Australia[92,93] and of pneumococcal disease in the US [94] were decreased or eliminated following vaccine introduction. Populations not targeted by the vaccine experienced reductions in morbidity and mortality associated with Hib disease [24,39,91,95-100], *Streptococcus pneumoniae* disease [43,83,101-107], meningococcal disease [3,9,108-114], hepatitis A [58], hepatitis B [115], typhoid fever [6], rotavirus diarrhea [116-123], human papilloma virus infection [124,125], and Japanese encephalitis [47]; these reductions were attributed to a herd protective effect.

The introduction of new vaccines has created interest in the development of diversified and innovative funding sources and mechanisms for vaccine introduction and sustainability. For example, innovative mechanisms such as bridge funding from the Vaccine Fund [49]; World Bank, UNICEF, USAID and WHO [42]; and the GAVI alliance [126] have accelerated and increased the coverage of new vaccines in low income countries. However, lack of financial planning impacted program sustainability in some countries [49,127].

### 3.8. Leadership and governance

New vaccine introduction impacted various aspects of the vaccine recommendation and regulatory processes. In Australia, Belgium, Canada, Chile, Greece, Taiwan, United Kingdom, United States, and Uruguay [4,21,27,39,128,129], existing national regulatory institutions and advisory committees were used to license and develop recommendations for new vaccines. Frequently, subcommittees were formed to develop recommendations for the specific vaccine, often in collaboration with academic pediatric and infectious disease organizations [39] and disease-specific societies[21,129].

Planning of vaccination campaigns has gone beyond the immunization program to include the departments of education, health, and defense; academic institutions and local

government [10,21]. In some countries, legislation was enacted to promote vaccine implementation or evaluation. For example, Italy had a law requiring routine infant HepB vaccination and catch-up vaccination of unvaccinated adolescents [130], and failure to comply had the potential to result in the temporary suspension of paternal authority to ensure immunization of the minor [131]. In Australia, legislation enabled the establishment of a national registry to collect data to assess HPV vaccination coverage [45].

#### 4. Discussion

In this comprehensive review of the published literature, we found that new vaccine introduction had a mixed effect on – and often provided opportunities to strengthen – existing components of the immunization system. Findings related to impact on the larger health system, however, were more limited. Few reviewed papers were designed to evaluate impacts on immunization systems or health systems, and information relevant to our review was often an incidental finding noted in the discussion section of the papers. In addition, most of the reviewed papers were from high- or middle-income countries, whose experiences may not represent those from lower-income countries, where the impact related to new vaccine introduction – both positive and negative – is likely to be greater. Our conclusions, therefore, need to be interpreted in the context of these caveats.

The impact of vaccine introduction differed according to the delivery platform and vaccine formulation. When vaccine introduction made use of existing delivery strategies, such as with routine infant immunization, costs and impact on staffing were substantially less than when vaccines were introduced through newly created platforms. School-based programs were documented to be effective platforms for introducing new vaccines to school-aged children and adolescents, although additional staff was required, even for existing programs. Venues outside the school were sometimes needed to complete the vaccination series in a timely fashion. Combination vaccines that added the new antigen or antigens to an existing vaccine were less costly and more efficiently introduced than those that required an additional injection.

Disruptions in routine vaccination services were reported, related to insufficient on-hand stock of the new vaccine when programs commenced, or to global vaccine shortages [132]. In low-income countries, service disruption also occurred due to vaccine program funding shortfalls, some of which were resolved through partner and donor contributions and infrastructure strengthening [22,37]. New vaccine introductions have highlighted existing gaps in logistics and cold chain systems; increased cold chain capacity needs were commonly reported with the introduction of the early formulations of RV vaccine [56,133]. As a result of early introduction experiences with inadequate infrastructure, effective vaccine management [134] assessments and regular cold chain inventories are now a precondition for new GAVI support in order to assure system readiness for the new vaccine. UNICEF has developed a new communication framework for new vaccine introduction that emphasizes cold chain readiness, improved adapted vaccines, presentations with reduced cold chain volumes, out-of-cold-chain use for outreach sessions, new delivery technologies, and enhanced training of health care workers [135]. A comprehensive assessment of cold chain capacity should be included in all pre-vaccine introduction assessments.

Reduced disease incidence following new vaccine introduction, which was primarily reported from high-income countries, led to declines in the use of vaccine preventable disease-related curative health services (Table 3). Less antibiotic use, reduced antimicrobial resistance, and herd immunity extended these benefits to populations not targeted by the vaccines. There was some evidence in high-income countries that new vaccine introduction was associated with less use of ambulatory and hospital services and reduced costs. An important benefit to the health system facilitated by new vaccine introduction has been the widespread use of AD syringes and awareness of the importance of injection safety [136,137].

In high income countries, existing infrastructures were utilized and often strengthened to provide information for vaccine introduction into the early childhood vaccine schedule. In some countries, established health information and disease surveillance systems were enhanced to collect data for policy development, program advocacy, and impact assessment. In other countries, new systems were developed to monitor vaccine safety, vaccine effectiveness, and coverage with vaccines administered to age groups beyond early childhood, such as HPV vaccine. These new or enhanced systems can be expanded and adapted to facilitate introduction of other vaccines, and to improve disease surveillance.

National immunization advisory committees, often referred to as National Immunization Technical Advisory Groups (NITAGs), assist Ministries of Health develop evidence-based decisions regarding vaccine and immunization policy, including the introduction of new vaccines [138,139]. While such committees are more common in high and middle income countries, they will likely play increasingly important roles in low-income countries. The importance of social mobilization for the public and training and education for health care workers was frequently noted. The introduction of new vaccines led to the establishment of legislation intended to improve vaccine delivery or program assessment, including mandatory newborn vaccination [131] or school entry laws and national vaccine registries.

This review was subject to a number of limitations. Although much of the information about the impact of new vaccine introduction is contained in the gray literature [132] only published papers were included in this review. We originally proposed to systematically rate the quality and strength of evidence presented in the reviewed articles according to the GRADE method [140,141]. However, because information related to the impact of new vaccine introduction was rarely the main focus of the studies, and because of differences in study design and specific data elements collected, we were unable to compare studies or evaluate data quality. Because most papers were from high-income countries, it is difficult to generalize those experiences to low-income countries, which often have weaker infrastructure, and require donor support to fund immunization programs. While changes in the immunization and health systems occurred in conjunction with new vaccine introduction, we recognize that other health initiatives occurring in the countries during the same time period may have also contributed to these changes. Although the majority of papers we reviewed were published during the past decade, we also included reports of introductions from more than 20 years ago, and these reports may be less relevant to current introductions of new vaccines. While it is likely that the impact of vaccine introduction on a

country's existing immunization and health system reflected the underlying system strength, evaluating this was beyond the scope of this review.

Donor funding for immunization programs in developing countries is not always consistent or predictable; however, in recent years, a number of new immunization funding mechanisms have been introduced to provide more stable vaccine financing, and will likely facilitate new vaccine introductions in the future. While new vaccine introduction often includes an assessment of disease burden and impact on morbidity and mortality, a component of future evaluations should include the systematic and objective assessment of how the vaccine introduction affects the country's immunization system and broader health system, especially in low-income countries.

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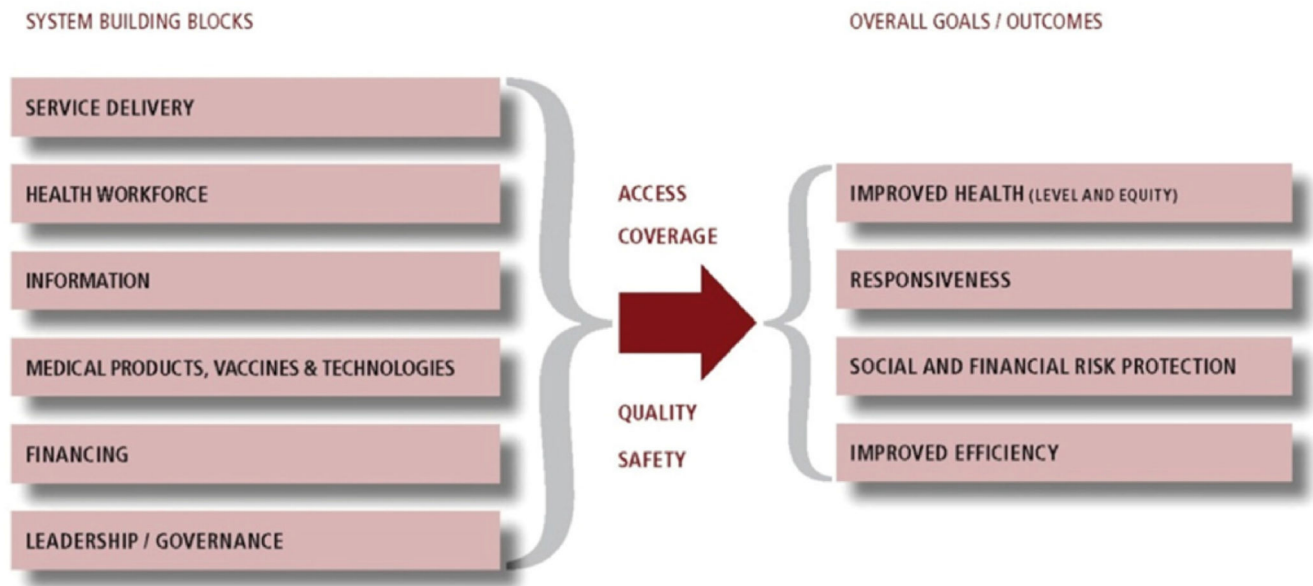
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## THE WHO HEALTH SYSTEM FRAMEWORK

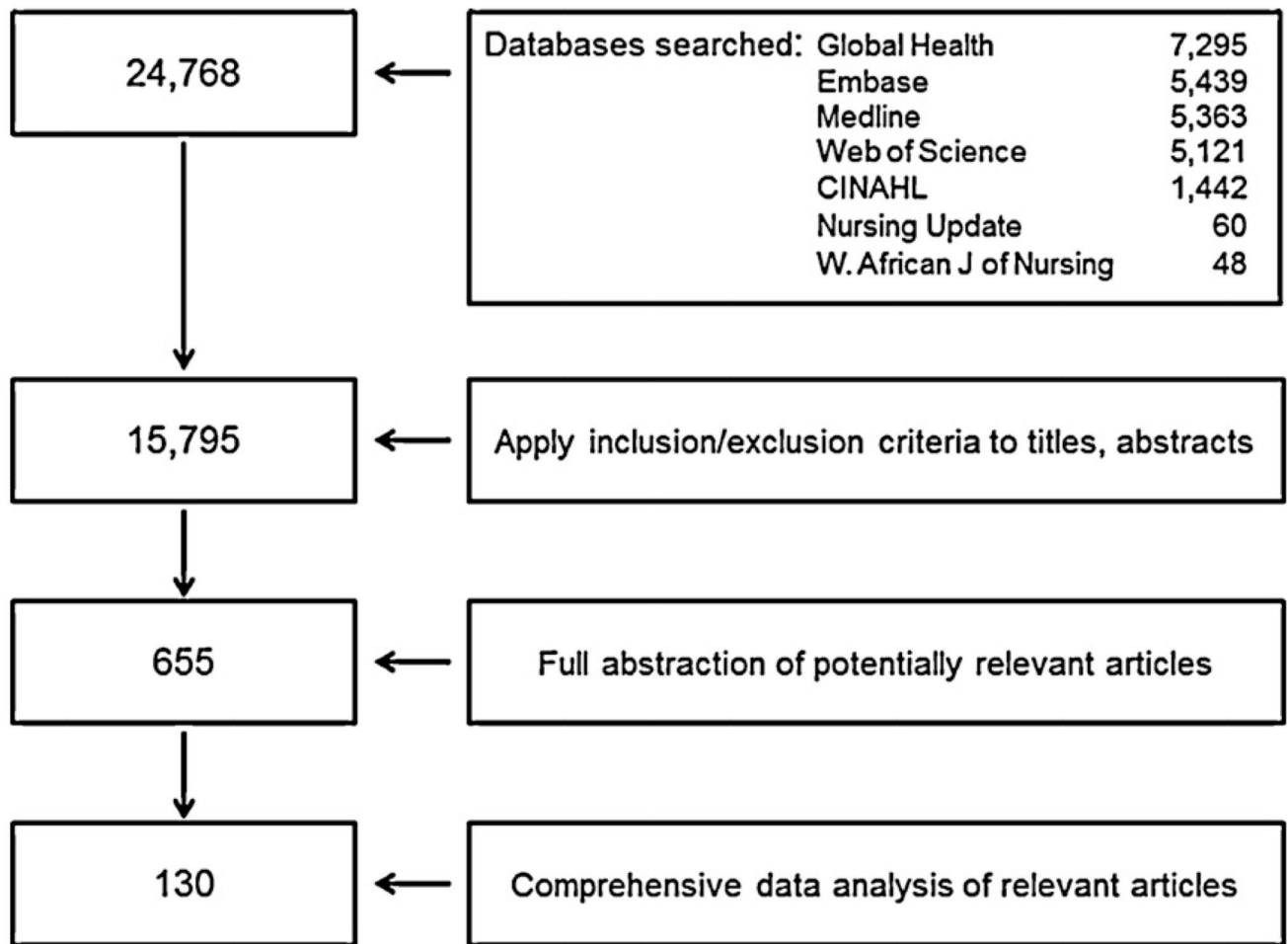


## THE SIX BUILDING BLOCKS OF A HEALTH SYSTEM: AIMS AND DESIRABLE ATTRIBUTES

- Good health **services** are those which **deliver** effective, safe, quality personal and non-personal health interventions to those who need them, when and where needed, with minimum waste of resources.
- A well-performing **health workforce** is one which works in ways that are responsive, fair and efficient to achieve the best health outcomes possible, given available resources and circumstances. I.e. There are sufficient numbers and mix of staff, fairly distributed; they are competent, responsive and productive.
- A well-functioning **health information system** is one that ensures the production, analysis, dissemination and use of reliable and timely information on health determinants, health systems performance and health status.
- A well-functioning health system ensures equitable access to essential **medical products, vaccines and technologies** of assured quality, safety, efficacy and cost-effectiveness, and their scientifically sound and cost-effective use.
- A good health **financing** system raises adequate funds for health, in ways that ensure people can use needed services, and are protected from financial catastrophe or impoverishment associated with having to pay for them.
- **Leadership and governance** involves ensuring strategic policy frameworks exist and are combined with effective oversight, coalition-building, the provision of appropriate regulations and incentives, attention to system-design, and accountability.

Fig. 1.  
Health systems framework.

Source: [2]. [http://www.who.int/healthsystems/strategy/everybodys\\_business.pdf](http://www.who.int/healthsystems/strategy/everybodys_business.pdf).



**Fig. 2.** Database search algorithm and review criteria used for systematic literature review of the impact of new vaccine introduction on the immunization and health systems.

**Table 1**

Search terms used for systematic literature review of the impact of new vaccine introduction on the immunization and health system.

<b>Vaccine search term category</b>	
1	exp *Hepatitis B Vaccines/
2	exp *Haemophilus Vaccines/
3	exp *Pneumococcal Vaccines/
4	exp *Rotavirus Vaccines/
5	exp *Meningococcal Vaccines/
6	exp *Yellow Fever Vaccine/
7	exp *Japanese Encephalitis Vaccines/
8	exp *Papillomavirus Vaccines/
9	exp *Typhoid-Paratyphoid Vaccines/
10	exp *Cholera Vaccines/
11	(HPV vaccine or HPV vaccines).ab,ti.
12	(HBV vaccine or HBV vaccines).ab,ti.
13	(hib vaccine or Hib vaccines).ab,ti.
14	new vaccine.ab,ti.
15	new vaccines.ab,ti.
16	((under utilised or under-utilised or under utilised or under-utilised or underutilised or underutilised) and (vaccine or vaccines)).ab,ti.
<b>Immunization and health system search term category</b>	
17	exp Immunization Programs/
18	health planning/or health care rationing/or health plan implementation/or health planning guidelines/or health planning technical assistance/or health priorities/or health resources/or national health programs/or exp regional health planning/
19	Capacity Building/
20	exp Inservice Training/
21	capacity building.ab,ti.
22	building capacity.ab,ti.
23	skill development.ab,ti.
24	“delivery of health care”/or health services accessibility/or healthcare disparities/
25	equity.ab,ti
26	“quality of health care”/or clinical competence/or guideline adherence/or exp “outcome and process assessment (health care)”/or program evaluation/or quality assurance, health care/or benchmarking/or clinical audit/or medical audit/or nursing audit/or total quality management/
27	health system.ab,ti.
28	health systems.ab,ti.
29	(health service or health services).ab,ti.
30	Health Manpower/
31	exp “Patient Acceptance of Health Care”/

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- 32 (community mobilisation or community mobilisation).ab,ti.
- 33 community advocacy.ab,ti.
- 34 information systems/or integrated advanced information  
management systems/or management information systems/or  
ambulatory care information systems/or clinical pharmacy  
information systems/or database management systems/or  
healthcare common procedure coding system/or "personnel  
staffing and scheduling information systems"/
- 35 safety.ab,ti.
- 36 systems integration/
- 37 employee incentive plans/or personnel loyalty/or "personnel  
staffing and scheduling"/or personnel turnover/or physician  
incentive plans/or "salaries and fringe benefits"/or workload/
- 38 Curriculum/
- 39 Forecasting/
- 40 Group Purchasing/
- 41 procurement.ab,ti.
- 42 logistics.ab,ti.
- 43 cold chain.ab,ti.
- 44 financial management/or exp budgets/or fund raising/or risk  
management/or financial support/
- 45 Health Services/
- 46 Health Personnel/
- 47 Social Change/
- 48 "Organization and Administration"/
- 49 Product Surveillance, Postmarketing/
- 50 medical waste/or medical waste disposal/
- 51 Decision Making, Organizational/
- 52 policy making/or advisory committees/
- 53 Government Regulation/
- 54 stock.ab,ti.
- 55 Immunologic Surveillance/
- 56 population surveillance/or sentinel surveillance/
- 57 (strain surveillance or serotype surveillance or virological  
surveillance or epidemiological surveillance).ab,ti.
- 58 access to services.ab,ti.
- 59 (affordability or affordable).ab,ti.
- 60 ((timeliness or timely) adj3 vaccination).ab,ti.
- 61 delivery strateg\*.ab,ti.
- 62 integrated disease control.ab,ti.
- 63 social mobilization.ab,ti.
- 64 (incentiv\* adj3 health care worker\*).ab,ti.
- 65 pre-training.ab,ti.
- 66 (in-service training or inservice training).ab,ti.
- 67 (career path or career paths).ab,ti.
- 68 wages.ab,ti.
- 69 supportive supervision.ab,ti.

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- 70 data quality.ab,ti.
  - 71 data collection.ab,ti.
  - 72 data management.ab,ti.
  - 73 health management information system.ab,ti.
  - 74 impact monitoring.ab,ti.
  - 75 adverse events following immunization.ab,ti.
  - 76 AEFI.ab,ti.
  - 77 (post marketing adj3 evaluation).ab,ti.
  - 78 (demand and supply forecasting).ab,ti.
  - 79 (demand adj3 forecasting).ab,ti.
  - 80 (supply adj3 forecasting).ab,ti.
  - 81 (stock\* adj3 manag\*).ab,ti.
  - 82 pooled procurement\*.ab,ti.
  - 83 (effective adj3 vaccine management).ab,ti.
  - 84 financing.ab,ti.
  - 85 (vaccine\* adj3 price\*).ab,ti.
  - 86 healthy market\*.ab,ti.
  - 87 fiscal space.ab,ti.
  - 88 budget support.ab,ti.
  - 89 (donor\* adj3 pool\*).ab,ti.
  - 90 SWAp.ab,ti.
  - 91 opportunity cost\*.ab,ti.
  - 92 (national regulatory agenc\* or national immunization technical advisory group\* or national immunisation technical advisory group\* or legislation or governance or accountability or inter-agency coordinating committee\* or interagency coordinating committee\*).ti,ab.
  - 93 ((treatment adj3 cost\*) or (hospitalization adj3 cost\*) or (hospitalisation adj3 cost\*) or (norms adj3 standards)).ti,ab.
  - 94 (storage adj3 capacity).ab,ti.
  - 95 (storage adj3 volume).ab,ti.
  - 96 (vaccine\* adj3 stor\*).ab,ti.
  - 97 (vaccine\* adj3 handl\*).ab,ti.
  - 98 (vaccine\* adj5 distribut\*).ab,ti.
  - 99 (vaccine\* adj5 transport\*).ab,ti.
  - 100 ((supply or supplies) adj5 (frequen\* or interval\*)).ab,ti.
  - 101 logistic\*.ab,ti.
  - 102 ((immunization adj3 expenditure\*) or (immunisation adj3 expenditure\*)).ab,ti.
  - 103 exp "health care economics and organizations"/
  - 104 (economics or legislation jurisprudence).fs.
-

**Table 2**

Literature cited according to World Bank income level, country, and vaccine(s) discussed for vaccines introduced 1980–2008.<sup>a</sup>

World Bank income level <sup>b</sup>	Country	No. of references	Vaccine(s) <sup>c</sup> [Reference]
High	Australia	10	Hib [92,93]; HPV [5,16,32,45,124]; PCV [30,106]; RV [123]
	Austria	1	RV [117]
	Belgium	1	HPV [128]
	Canada	14	HepB [18,25]; Hib [24,95]; Influenza [70]; MenPS/Conj [9,110-112]; PCV [17,43,77,78]; PPV23 [52]
	Finland	1	Hib [66]
	Germany	2	HAV [12]; PCV [102]
	Great Britain	13	Hib [26,62,96]; HPV [23,34]; MenPS/Conj [4,7,28,109,113,114]; PCV [72]; PPV23 [33]
	Greece	1	HepB [129]
	Israel	2	Hib [29,91]
	Italy	9	HepB [41,79,89,130,131,137]; PCV [88]; PPV23 [87], RV [75]
	New Zealand	1	MCV-B [46]
	Singapore	1	HBV [19]
	Spain	3	HAV/HepB [58]; Hib [97]; MenPS [108]
	Sweden	1	Hib [31]
	Taiwan	4	HepB [21,80,81,115]
	USA	28	Combo (DTP/Hib/HepB/IPV) [54]; Hib [85]; HPV [35]; PCV [11,59-61,63-65,67,68,71,74,83,86,90,94,101,103,104,107]; PPV23 [76]; RV [86,119-122]
	Multiple countries <sup>f</sup>	1	Hib [69]
	Multiple countries <sup>g,h,i</sup>	3	HPV [8,27,125]
Total high income country refs. (% of total)		96	(75)
Middle	Brazil	1	RV [82]
	Chile	1	Hib [53]
	Cuba	1	Hib [98]
	Egypt	1	MenPS [3]
	El Salvador	1	RV [118]
	Indonesia	1	Typhoid [10]
	Mexico	1	RV [116]
	Nicaragua	1	RV [51]
	Peru	1	HepB [15]
	People's Republic of China		HepB [20,36,48]; JE [47]; HAV/JE [38]
	Senegal	1	Combo (DTP/Hib/HepB/IPV) [99]
	South Africa	2	HepB [44]; Hib [50]
	Thailand	1	HepB [13]

World Bank income level <sup>b</sup>	Country	No. of references	Vaccine(s) <sup>c</sup> [Reference]
	Multiple countries <sup>j,k</sup>	1	Hib [39]
	Multiple countries <sup>l</sup>	1	Typhoid [6]
	Multiple countries <sup>m</sup>	1	RV [56]
Total middle income country refs (% of total)		21	(16)
Low	Ethiopia	1	Combo (DTP/Hib/HB/IPV) [42]
	Gambia	1	Hib [55]
	Malawi	1	Hib [49]
	Zimbabwe	1	HepB [37]
Total low income country refs. (% of total)			(3)
Not classified <sup>d</sup>	18 European countries	1	HPV [57]
	50 GAVI-eligible countries	1	HepB & Hib [126]
	Americas	1	Hib [41]
	Multiple countries <sup>n,o</sup>		Hib [22,127]
	Global	1	HepB [14]
	Global <sup>p</sup>	1	Hib [100]
Total not classified refs. (% of total)		7	(5)
Literature review	Multiple countries <sup>q</sup>	1	PCV[73]
Total literature reviews (% of total)		1	(0.8)
Total refs		129 <sup>e</sup>	

<sup>a</sup>Year of vaccine introduction (number [%] of references): 1980–1989 – 14(12%); 1990–1999 – 37 (32%); 2000–2007 – 64 (56%); 115/129 (89%) specified studies the year of introduction.

<sup>b</sup>Based on Gross National Income (GNI) per capita. Low: <USD1005; middle: USD1006–12,275 (includes lower middle [USD1006–3975] and upper middle [USD3976–12,275]); high: >USD12,276.

<sup>c</sup>Diphtheria–tetanus–pertussis (DTP), hepatitis A (HAV) vaccine, hepatitis B (HepB) vaccine, *Haemophilus influenzae* type B (Hib) vaccine, human papillomavirus (HPV) vaccine, inactivated polio vaccine (IPV), Japanese Encephalitis (JE), meningococcal polysaccharide (MenPS) vaccine, meningococcal conjugate vaccine type B (MCV-B) pneumococcal conjugate vaccine (PCV), 23-valent pneumococcal polysaccharide vaccine (PPV-23), and rotavirus (RV) vaccine.

<sup>d</sup>Studies done in multiple countries with different World Bank income levels.

<sup>e</sup>1 reference identified by the authors and not by the literature search for inclusion is not included in the table [136].

<sup>f</sup>Finland, Iceland, Germany, Switzerland.

<sup>g</sup>USA & Canada.

<sup>h</sup>USA, Puerto Rico, Canada.

<sup>i</sup>Italy & Belgium.

<sup>j</sup>Chile & Uruguay.

<sup>k</sup>South Africa & Argentina.

<sup>l</sup>Thailand, China, Vietnam, India, Indonesia, Pakistan.

<sup>m</sup>Brazil, Ecuador, El Salvador, Panama, Mexico, Nicaragua, Venezuela.

<sup>n</sup>Ghana, Mozambique, Tanzania, Lesotho.

<sup>o</sup>Qatar, Uruguay, Chile, Kuwait.

<sup>p</sup>US Army beneficiaries.

<sup>q</sup>US, UK, Norway, Netherlands, Germany, Canada, Switzerland, Spain, Australia.

**Table 3**

Impact on health care utilization and economic impact (where documented) following new vaccine introduction in selected countries.

Vaccine(s)	Outcome(s)	Country(ies)	Reference(s)	Reported economic impact
HepB <sup>a</sup>	Decrease in acute hepatitis B; hepatocellular carcinoma, HBV-associated glomerulonephritis	Italy, South Africa, Taiwan	[44,79-81,89]	Estimated US\$224M savings in acute health care costs [79,89] per year
Hib	Decrease in ambulatory consultations and hospitalizations for meningitis, epiglottitis, orbital and periorbital cellulitis and septic arthritis; change in empiric antibiotic recommendations	Gambia, Sweden, Finland, Wales, US, Iceland, Germany, Switzerland, Canada, UK, Netherlands, Australia, New Zealand	[31,55,62,66,69,85]	Modeled cost savings to society [31]
Influenza	Decrease in hospitalizations	Canada		[70]
PCV7, 10,13	Fewer antibiotic-resistant infections; decrease in hospitalizations for pneumonia, outpatient and emergency department visits for otitis media, pneumonia, and other respiratory infections, fever; invasive pneumococcal disease in HIV-infected persons; decrease in antibiotic prescriptions, insurance claims for otitis media, tympanostomy tube placement; change in recommendations for fever evaluation among vaccinated children	US, Canada, Italy, England, multi-country literature review	[59,61,63-65,67,68,71-74,77,78,83,86,88]	Vaccine cost-effective, and in some cases, cost-saving [83]
PPV23	Decrease in otitis media and pneumonia	Italy, US	[76,87]	Vaccination cost-saving [87]
RV	Decrease in hospitalizations, outpatient and emergency department visit for all-cause and rotavirus gastroenteritis	Brazil, Italy, US	[60,75,82,84]	Decreased curative health care costs [60,75,82]; increase [82] or no decrease [75,75] in health system costs.

<sup>a</sup> Hepatitis B (HepB), *Haemophilus influenzae* type b (Hib), pneumococcal conjugate vaccine (PCV), 23-valent pneumococcal polysaccharide vaccine (PPV23), rotavirus (RV).